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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
JALLA, SANJOO	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 04/20/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/618,134	SCHULER ET AL.	
	Examiner	Art Unit	
	Sanjoo Shree Jalla	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *9-11,29 and 30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9-11 and 29-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment, filed 4/3/06, is acknowledged.

   Claims 9-11 and 29-30 are pending.

   Applicant's election without traverse of group IV, claims 9-11 and 29-30, in the reply filed on 4/3/06 is acknowledged.

   Claims 9-11 and 29-30 are under consideration in the instant application.

2. Applicant's IDS, filed 7/11/03 is acknowledged.

3. Claim 9 is objected to because of the following informalities: The recitation "energizing" is misspelled. The correct spelling is "anergizing". Appropriate correction is required.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

   > *The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.*

   Claim 30 is rejected under 35 U.S.C. 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed. This is a new matter rejection.

   The specification and the claims as originally filed do not provide support for the invention as now claimed, specifically:

   Tr1-like regulatory cells inhibit the proliferation of syngeneic CD4+ T cells in claim 30.

   A review of the specification fails to reveal support for the new limitations.

   The specification (pages 9, 2nd paragraph, line 3) discloses "syngeneic CD4+ T cells could be markedly **decreased** by anergized $CD4^{+}CD25^{-}$ T cells" but the specification as filed does not appear to provide a clear support for the limitation of claim 30, where Tr1-like regulatory cells **inhibit** the proliferation of syngeneic $CD4^{+}$ T cells. "**Decrease**" and "**inhibit**" differ in their scope. For example, something that is inhibited cannot be up regulated.

5. Claims 9-11 and 29-30 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of

the claimed invention.

Applicant is in possession of a method for producing Tr1-like regulatory cells, comprising anergizing $CD4^+CD25^-$ T cells by contacting the $CD4^+CD25^-$ T cells with $CD4^+CD25^+$ T cells *ex vivo* or *in vivo.*

Applicant is not in possession of a method for producing Tr1-like regulatory cells, comprising aenergizing $CD4^+CD25^-$ T cells by contacting with any other anergic state inducing agent other than $CD4^+CD25^+$ T cells or a substance or a mixture of substances mimicking the role of $CD4^+CD25^+$ T cells ex vivo or in vivo.

The claimed invention is drawn to a genus of "anergic state inducing agent" and an anergic state inducing agent comprises $CD4^+CD25^+$ T cells and "a substance" and "a mixture of substances mimicking the role of $CD4^+CD25^+$ T cells". However the applicant has not disclosed all "anergic state inducing agent" and all anergic state inducing agent comprises $CD4^+CD25^+$ T cells and "a substance" and "a mixture of substances mimicking the role of $CD4^+CD25^+$ T cells" that can be used for producing Tr1-like regulatory cells and no structural identifying characteristics of the genus are disclosed. Therefore, the skilled artisan cannot envision all the contemplated "anergic state inducing agent" and "all anergic state inducing agent comprises $CD4^+CD25^+$ T cells" and "a substance" and "a mixture of substances mimicking the role of $CD4^+CD25^+$ T cells" recited in the instant claims. Consequently, conception cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred. Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC1993). The Guidelines for the Examination of Patent Application Under the 35 U.S.C.112, ¶ 1"Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 20001, see especially page 1106 3rd column).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.
Applicant is directed to the final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

6. Claims 9-11 and 29-30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

A method for producing Tr1-like regulatory cells, comprising anergizing $CD4^+CD25^-$ T cells by contacting the $CD4^+CD25^-$ T cells with $CD4^+CD25^+$ T cells *ex vivo* or *in vivo*.

Does not reasonably provide enablement for:

A method for producing Tr1-like regulatory cells, comprising anergizing $CD4^+CD25^-$ T cells by contacting with any other anergic state inducing agent other than $CD4^+CD25^+$ T cells or or any substance or any mixture of substances mimicking the role of $CD4^+CD25^+$ T cells ex vivo or in vivo.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims because of the following reasons:

The specification disclosure is insufficient to enable one skilled in the art to practice the invention as claimed without an undue amount of experimentation. Undue experimentation must be considered in light of factors including: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill in the art, the level of predictability of the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention, see In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) states, "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art". The " amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling" (MPEP 2164.03). The MPEP further states that physiological activity can be considered inherently unpredictable. With these teachings in mind, an enabling disclosure, commensurate in scope with the breadth of the claimed invention, is required.

The specification does not disclose "anergic state inducing agent" or "anergic state inducing agent comprises $CD4^+CD25^+$ T cells" or "a substance" or "a mixture of substances mimicking the role of $CD4^+CD25^+$ T cells". The term "anergic state inducing agent" and "anergic state inducing agent comprises $CD4^+CD25^+$ T cells" and "a substance" and "a mixture of substances mimicking the role of $CD4^+CD25^+$ T cells" encompasses in their breadth any other anergic state inducing agent other than $CD4^+CD25^+$ T cells and any substance and any mixture of substances mimicking the role of $CD4^+CD25^+$ T cells. It is well known in the art at the time the invention was made that an anergic state inducing **agent or a substance** as recited could be an amino acid or a peptide or a small molecule or even an atom. Further, it is well known in the art that minor structural differences among structurally related compounds can result in substantially different pharmacological

activities and that the molecules having lightly diverse structural and biochemical properties can function agonist and antagonists. For example, Huang (Pharmacol. Therapeutics 2000: 86: 201-215) in his review article notes the daunting task faced by the skilled artisan in developing small molecule regulators of protein-protein interactions, and describes that the process required long periods of trial and error testing before suitable compounds could be developed ("Introduction" section on page 202). Similarly, even single amino acid differences can result in drastically altered functions between two proteins. It is noted by Metzler et al. (Nature Structural Biol. 1997; 4:527-531) that any of a variety of single amino acid changes can alter or abolish the ability of CTLA4 to interact with its ligands CD80 and C1786 (e.g., summarized in Table 2). Further, it is noted by Taylor et. al. (Microbes and Infection 2005; 7: 1049-1055) that combining vitamin D3 with dexamethasone in vitro, induces human and mouse naïve $CD4^+$ T cells to differentiate into Tr1 cells (inducible T regulatory cells). However, these cell only produce IL-10 and not IL-5 or IFN-δ like other $CD4^+$ T cells (see in particular page 1051, right hand column, section 2.2). Further, Taylor et. al. note that the development and activation of different T regulatory cell populations in human and in *in vivo* experimental model requires further investigation (see in particular page 1053, right hand column, section 2.5). In the absence of working examples or detailed guidance in the specification, the intended uses of any **agent or a substance or a mixture of substances**, such as a simple or complex organic or inorganic molecule, a peptide, a protein (e.g. antibody), an oligonucleotide (e.g. anti-sense) are fraught with uncertainties.

Further, the method of producing Tr1-like regulatory cells comprising anergizing $CD4^+CD25^-$ T cells by contacting the $CD4^+CD25^-$ T cells with an anergic state inducing agent that comprises $CD4^+CD25^+$ T cells is an open ended language which encompasses addition of unrecited elements. The specification does not disclose, besides $CD4^+CD25^+$ T cells, what else the anergic state inducing agent encompasses. Therefore, the method of the claims cannot likely function as broadly claimed. Accordingly, the method of producing Tr1-like regulatory cells as broadly claimed must be considered highly unpredictable. Given said unpredictability, the method of the instant claims must be considered to require undue experimentation.

Further, the structure of such "any anergic state inducing agent" or "any substance" or "any mixture of substances mimicking the role of $CD4^+CD25^+$ T cells", cannot be readily envisioned by one of skill in the art based upon the guidance provided in the specification as filed. Therefore, the applicant does not provide a sufficiently enabling disclosure regarding production of Tr1-like regulatory cells comprising contacting $CD4^+CD25^-$ T cells with any other anergic state inducing agent other than $CD4^+CD25^+$ T cells or any substance or any mixture of substances mimicking the role of $CD4^+CD25^+$ T cells.

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. Without sufficient guidance, the structural features of "any other anergic state inducing agent other than $CD4^+CD25^+$ T cells" or "any substance" or "any mixture of substances mimicking the role of $CD4^+CD25^+$ T cells" are unpredictable; thus the experimentation left to those skilled in the art, is unnecessarily, and improperly, extensive and undue.

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this office action:

A person shall be entitles to a patent unless-

> *(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.*
>
> *(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.*

Claims 9-11 and 29-30 are rejected under 35 U.S.C. 102 (a) as being anticipated by Dieckmann et. al. (J. Exp. Med. July 15, 2002; 196: 247-253).

Dieckmann et. al. teach a method for producing $CD4^+CD25^-$ T cells i.e. Tr1-like regulatory cells (see in particular abstract) comprising contacting $CD4^+CD25^-$ T cells with $CD4^+CD25^+$ T cells (i.e. with an anergic state inducing agent) *ex vivo*, wherein, co culturing of $CD4^+CD25^-$ T cells with $CD4^+CD25^+$ T cells results in high level IL-10 production (see in particular page 249, Figure 1). Dieckmann et. al. further teach that $CD4^+CD25^-$ T cells i.e. Tr1-like regulatory cells suppress i.e. inhibit the proliferation of syngeneic CD4+ T cells (see in particular, abstract).

The reference teaching anticipates the claimed invention.

8. Claims 9-11 and 29-30 are rejected under 35 U.S.C. 102 (b) as being anticipated by Thornton et. al. (The Journal of Exp. Med. 1998; 188: 287-296).

Thornton et. al. teach coculturing $CD4^+CD25^+$ cells with $CD4^+CD25^-$ cells (i.e. *ex vivo*)(see in particular page 289, right hand column, last line and page 290, left hand column, 1st line). While Thornton et. al. do not explicitly teach a method for producing Tr1-like regulatory cells, however, since the claimed steps of the method for producing Tr1-like regulatory cells i.e. the step of contacting $CD4^+CD25^-$ cells with $CD4^+CD25^+$ cells, is the same as the reference method step, the reference method would inherently result in production of Tr1-like regulatory cells (instant claims 9-11) wherein said Tr1-like regulatory cells produce IL-10 (instant claim 29) and inhibit the proliferation of syngeneic CD4+ T cells (instant claim 30).

The reference teaching anticipates the claimed invention.

9. No claim is allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sanjoo Jalla whose telephone number is (571) 272-4453. The examiner can normally be reached Monday through Friday from 8:00 am to 5:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

11. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be

obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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